Indonesian Journal of Biotechnology, December, 2006 Vol. 11, No. 2, pp. 908-913

The Efficacy of Fucoidan on Gastric Ulcer

Mohammad Juffrie[1*], Ina Rosalina[2], Wahyu Damayanti[1], Ali Djumhana[3], Ariani[1], Harjono Ahmad[4]

[1]Department of Pediatrics, Faculty of Medicine, Gadjah Mada University, Yogyakarta, Indonesia.
[2]Department of Pediatrics, Faculty of Medicine, Padjadjaran University, Bandung, Indonesia.
[3]Department of Internal Medicine, Faculty of Medicine, Padjadjaran University, Bandung, Indonesia.
[4]Department of Internal Medicine, Faculty of Medicine, Brawidjaya University, Malang, Indonesia.

Abstract

Hyperacidity causes gastric injury, and in severe situations, ulcer could develop. The growth factors known as the basic fibroblast growth factor (bFGF) and the epidermal growth factor (EGF) have been recognized to promote ulcer healing. Fucoidan is extracted from a brown seaweed of Okinawa called Mozuku or Cladosiphon okamuranus. Fucoidan is effective for the healing of gastric ulcers by inducing epithelial cells to produce growth factors. The aim of this study is to explore the efficacy of fucoidan in patient who suffered by gastric ulcer. A randomized control trial double blind was conducted to 33 eligible samples. By using four-blocks random samples were divided into fucoidan and placebo groups. 100 mg of fucoidan was given to the fucoidan group and 100 mg of glucose was given to the placebo group. Due to ethical reasons, for both groups were given a proton pump inhibitor. There was no difference in the age category between the fucoidan group (mean: 46.23 ± 14.8 years) and the placebo group (mean: 46.18 ± 18.4 years) (*p*: 0.28). There was also no difference in sex between the fucoidan group (female: 10 / 33; male 7 / 33) and the placebo group (female: 7 / 33; male: 9 / 33); *p*: 0.38. According to the SAKITA and MIWA criterias 32 patients fulfilled A1 which indicate active severe ulcer, and 1 patient fulfilled A2 which indicate active moderate ulcer. Most of the ulcers were gastric ulcer. There was a significant improvement of the grade of ulcer in fucoidan group (94%) (16 / 17) compared to placebo group (37.5%) (6 / 16,*p*: 0.005). There was a significant reduction of abdominal pain after 5 days in the fucoidan group, compared to the placebo group (*p*: 0.04). Vomiting tends to decrease in day 6 of the fucoidan group however its proportion is similar with that of the placebo group (*p*: 0.9). Fucoidan is effective for ulcer healing and reducing ulcer symptoms.

Key words : fucoidan, gastric ulcer, anti-peptic activity

Introduction

Gastric epithelial cells secreted a proteoglycan called mucin which protectsthe gastric mucosa from acid and pepsin. Sulfated polysaccharides as known as sulfomucins are reported to exert antipeptic activity by ionic binding of gastric surface proteins (Takagaki and Hota, 1979).

*Corresponding author: Mohammad Juffrie, Department of Pediatrics, Faculty of Medicine, Gadjah Mada University, Jl. Kesehatan No.1, Yogyakarta 55281, Indonesia. E-mail: juffrie@indosat.net.id

In situations where the gastric is injured by hyperacidity, epithelial cells or submucosal cells produced growth factors that stimulate cell proliferation and repair the gastric injury. The growth factors known as the basic fibroblast growth factor (bFGF) and epidermal growth factor (EGF) have been recognized to promote ulcer healing (Szabo *et al*., 1995).

Fucoidan is a complex sulfated polysaccharide, derived from marine brown algae (Nishino *et al*., 1991a). Fucoidan is also an acid polysaccharide characterized by the main constituents of fucose and sulfate radical and galactose, xylose or uronic acid

is contained as constituent sugar depending on the seaweed species (Berteau *et al.*, 2003).

The fucoidans from brown seaweed mediate a variety of significant biological effects on mammalian cells and have many biological activities such as anticoagulant (Bernardi and Springer, 1962), activators antithrombin III and heparin cofactor (Nishino *et al.*, 1991b), inhibit initial binding of sperm for penetration of the human pellucida zone (Mahoni *et al.*, 1991), blocks the infection of human cells line in several viral infection, HIV, herpes and cytomegalovirus, and cells binding, and also demonstrates differential binding of some inflammatory mediators (Foxall *et al.*, 1992). In particular, fucoidan is effective for ulcer healing of gastric ulcers. Some studies demonstrate anti ulcer effect of fucoidan by induce epithelial cells to produce growth factors (Szabo *et al.*, 1995).

In the present study, we therefore explore the efficacy of fucoidan in patients who suffered from gastric ulcer.

Subjects and Methods

The subjects of this study are patients who attended to the out patients or in patients in the subdivision of Gastroenterology, Pediatrics Department and the Department of Internal Medicine, Sardjito Hospital, Yogyakarta; Hasan Sadikin Hospital Bandung and Syaiful Anwar Hospital, Malang, Indonesia during 2004-2006. The inclusion criteria are patients with the age of at least eight years with abdominal pain or dyspepsia according to the dyspepsia criteria scale, and during the last month did not consumed any anti ulcer drugs.

All patients who fulfilled the criteria underwent a first endoscope. In the first endoscope the patients who had ulcer were included in the study and patients who had Helicobacter Pylori infection and gastric cancer were excluded from the study. The subjects agreed to be involved in the study by signing an informed consent. Ethical Clearance was adjusted by the Medical Ethic Committee from the Faculty of Medicine, Padjadjaran University, Bandung, Indonesia. Patients eligible for the study were randomly allocated using four-steps block random, and then they were divided into the fucoidan group and placebo group. After three weeks of receiving fucoidan or placebo, the patients underwent a second endoscope to evaluate the ulcer. Biopsies of gastric and duodenal mucosa were obtained during endoscopes and specimens were sent to the pathologist. The severity of the ulcer was diagnosed referring to the SAKITA and MIWA criteria (Takemoto *et al.*, 1991) as shown in Table 1.

Table 1. Sakita and Miwa classification

Stage		Endoscope finding
Active stage	A1	Punched-out ulcer with swollen periphery due to edema and the bottom covered with thick lichen and bleeding and coagulated massed are detectable
	A2	Edema becomes mild and the bottom of the ulcer is covered with white lichen
Healing Stage	H1	Ulcer is reduced with a red zone due to regenerated epithelium in the periphery. Accumulation of mucosal folds is observable
	H2	Ulcer is reduce further with widening of the peripheral red zone and clear accumulation of mucosal folds
Scarring Stage	S1	White lichen has disappeared and redness is observed in the center of the mucosal fold accumulation
	S2	Redness has disappeared leaving only accumulation of mucosal folds

A: Active stage; H: healing stage; S: scarring stage

The fucoidan group received 100 mg of fucoidan a day for three weeks. This fucoidan is extracted from the Okinawa brown seaweed called Mozuku or Cladosiphon Okamuranus. The structure of the fucoidan is a high molecular polysaccharide on a base unit of fucose, part of which is bounded to uronic acid.

The placebo group received placebo which consist of glucose. The fucoidan and placebo were packed into a capsule in the same size and same color. A proton pumpinhibitor was given to fucoidan and placebo group for ethical reason. During the three weeks, patients consumed the fucoidan and placebo; they were followed

up regarding clinical symptoms and signs according to the case report form. All data were analyzed using computer analyzing program SPSS version 12. The difference between fucoidan and placebo group was calculated using the chi-square analysis program for proportional data. The difference between the means was calculated using a student t test analyzing program.

Results

Thirty three samples were included in the study, 17 patients were in the fucoidan group and 16 patients were in the placebo group (*p*: 1). Distended in days 4 tended to decrease in fucoidan group. There was no difference in age category between fucoidan group (mean: 46.23 ± 14.8 years) and placebo group (mean: 46.18 ± 18.4 years) (*p*: 0.28) (Table 2). There was no difference in the gender category between fucoidan group (female: 10/33; male 7/33) and placebo group (female: 7/33; male: 9/33); *p*: 0.38 (Table 3).

Table 2. Age distribution

Group	N	Mean of age	St. Deviation	p
Fucoidan	17	46.23	14.84	0.28
Placebo	16	46.18	18.41	

Table 3. Sex distribution

Group	Sex		Total	P
	Female	Male		
Fucoidan	10	7	17	0.38
Placebo	7	9	16	

Table 4. Diagnosis of ulcer according to SAKITA and MIWA before treatment

Group	Sex		Total	P
	Female	Male		
Fucoidan	10	7	17	0.38
Placebo	7	9	16	

According to the SAKITA and MIWA criteria 32 patients fulfilled A1 category, which indicate active severe ulcer, and one patient fulfilled A2 which indicate active moderate ulcer (Table 4, Figure 1). Most of the ulcers are gastric ulcer. There was significant improvement of grade of the ulcer in the fucoidan group 94% (16/17) compareto the placebo group 37.5% (6/16) Table 5, Figure 2. (*p*: 0.005).

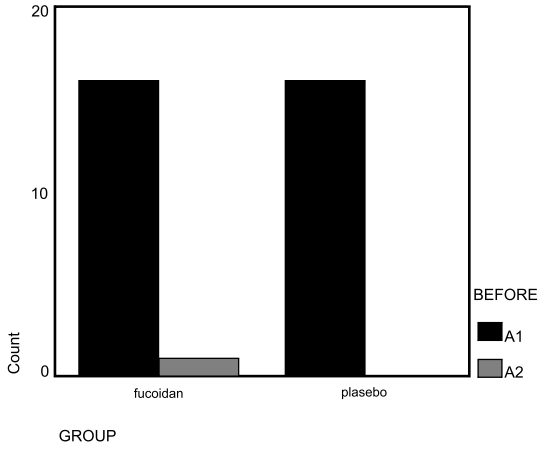

Figure 1. Bar chart of diagnosis ulcer before treatment

Table 5. Diagnosis of ulcer after treatment

	SAKITA						Total
GROUP	No change	change A1 to A2	change A1 to H3 or A2 to H4	change A1 to H2	Change A1 to S1	Change A1 to S1	
Fucoidan	0	2	11	2	1	1	17
placebo	10	0	4	1	1	0	16
Total	10	2	15	3	2	1	33

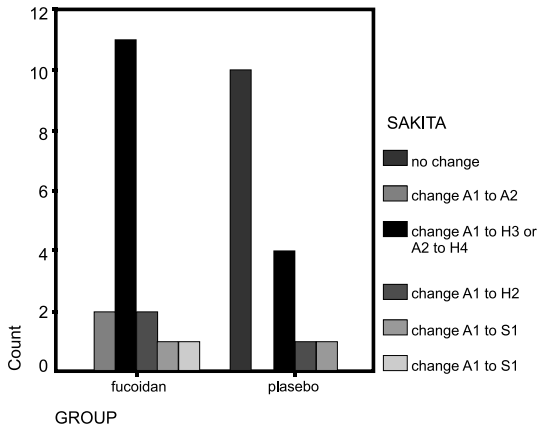

Figure 2. The diagnosis of ulcer acording to Sakita and Miwa after treatment

There was significant reduction of abdominal pain after five days in the fucoidan group compared to the placebo group (*p*: 0.04; Figure 3). In addition, vomiting tends to decrease in days 6 in the fucoidan group (Figure 4). However, its the proportion is similar with that in placebo group (*p*: 0.9). Distended was significant decreased in days 3 in the fucoidan group, compared to that in the placebo group (*p*: 0.02, Figure 5).

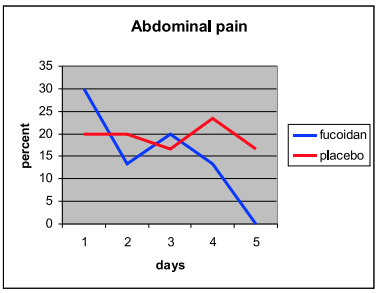

Figure 3. Abdominal pains after 5 days observation

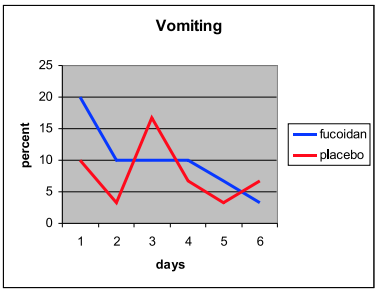

Figure 4. Vormiting after 6 days observation

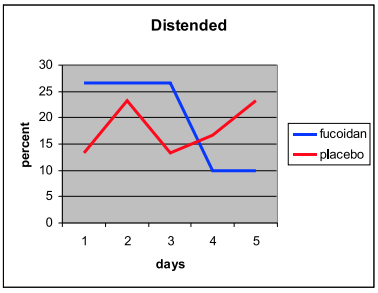

Figure 5. Distended after 5 days observation

Discussion

This study explored the efficacy of fucoidan in gastric ulcer. Fucoidan significantly have effects ulcer healing, compared to those in without fucoidan. The symptoms of dyspepsia were reduced significantly after days 5-6 days of consuming fucoidan. Incidence of gastric ulcer is only slightly higher among men and around 5% to 10% of the population (Soll, 1989).

In acute gastritis there is erosion and damage to the gastric mucosa. If the erosion is deep and this damage is distributed in focal area through the mucosa and in some cases through the submucosa then gastric ulcer could occur. The damage generally occur in the setting of a serious systemic illness such as trauma, burns, sepsis, liver and renal failures and shock, or with certain drugs such as non-steroid anti inflammatory drugs (Soll, 1990).

This study showed that most of the patients (94%) with severe gastric ulcers (active stage) who received fucoidan 100 mg a day for three weeks changed to the healing stage or scarring stage. In contrast, patients who receive placebo only 37.5% changed to the healing stage. This indicates that fucoidan is strongly has anti gastric ulcer effects.

Fucoidan from Cladosiphon Okamuranus is known to have anti ulcer effects. Some studies have demonstrated that fucoidan has anti-ulcer effects. Using acetic acid induced gastric ulcer and indomethacin induced gastric erosion models in rat (Shibata *et al.*, 1998), it was suggested that the fucoidan from Cladosiphon binds proteins, inhibits peptides activity and prevent the bFGF instability, which should results in an anti-ulcer effect. In agreement herewith, a study using hemoglobin and BSA as substrate demonstrated that fucoidan from Cladosiphon Okamuranus is a sulfated polysaccharide with a potent anti-ulcer activity by preventing peptic digestions

(Shibata *et al.*, 2000). The anti-peptic effects of sulfate polysaccharide were due to their anionic change and to the ionic binding to the protein substrate. The lackof inhibition with a low molecular weight synthetic substrate N-acetylphenylalanyl diiodotyrosine showed that the effect is not on the enzyme itself (Shibata *et al.*, 2000).

In addition, Cladosiphon fucoidan does not stimulate superoxide generation and TNFá secretion by inflammatory cells. It means that Cladosiphon fucoidan did not show any inflammatory effect (Shibata *et al.*, 2000).In concern with gastric mucosal protection, Cladosiphon fucoidan has an effect on the bFGF stabilizing activity (Folkman *et al.*, 1991; Ornitz *et al.*, 1995; Chintala *et al.*, 1994; Faham *et al.*, 1996; Shibata *et al.*, 2000). The studies showed that this sulfated polysaccharides stabilize bFGF by binding to the peptide. The stabilized bFGF activity work on the pH 7.4 and pH 4.0 (Shibata *et al.*, 2000). As a study in patients who had gastric ulcer, this study proved that all effect of fucoidan occur in the patient.

This study also showed that the clinical symptoms of gastric ulcer, abdominal pain,vomiting and abdominal distended were reduced 3-4 days after receiving fucoidan Cladosiphon. These observations reflected on the correlation between effects of ulcer healing towards the clinical symptoms of the gastric ulcer.

Conclusion

Cladosiphon fucoidan has an effect on anti-ulcer in patients with gastric ulcer.

Acknowledgment

The authors would like to thank Meiji Seika Kaisha Ltd and Toyo Science Corporation for supporting writing this paper.

References

Bernardi, G., and Springer, G.F., 1962, Properties of highly purified fucan. *J. Biol. Chem.*, 237, 75–80.

Berteau, O., and Mulloy, B., 2003, Sulfated fucans, fresh perspectives: structures, functions, and biological properties of sulfated fucans and an overview of enzymes active toward this class of polysaccharide. *Glycobiology*, 13 (6), 29R-40R.

Chintala, S.K., Millar, R.R., and McDevitt, C.A., 1994, Basic fibroblast growth factor binds to heparin sulfate in the extracellular matrix of rat growth plate chondrocytes. *Arch. Biochem. Biophys.* 310, 180-186.

Faham, S., Hileman, R.E., Fromm, J.R., Linhardt, R.J., and Rees, D.C., 1996, Heparin structure and interactions with basic fibroblast growth factor. *Science,* 271, 1116-1120.

Folkman, J., Szabo, S., Stovroff, M., McNeil, P., Li, W., and Shing, Y., 1991, Duodenal ulcer. Discovery of a new mechanism and development of angiogenic therapy that accelerates healin. *Ann. Surg.*, 214, 414-427.

Foxall, C., Watson, S.R., Dowbenko, D., Fennie, C., Lasky, L. A., Kiso, M.,

Hasegawa, A., Asa, D., and Brandley, B.K., 1992, The three members of the selectin receptor family recognize a common carbohydrate epitope, the sialyl Lewis(x) oligosaccharide. *J. Cell. Biol.*, 117 (4), 895–902.

Mahony, M.C., Oehninger, S., Clark, G.F, Acosta, A.A., and Hodgen, G.D., 1991, *Contraception*, 44, 657-665.

Nishino, T., Kiyohara, H., Yamada, H., and Nagumo, T., 1991a, An anticoagulant fucoidan from the brown seaweed Ecklonia kurome. *Phytochemistry*, 30, 535-539.

Nishino, T., Aizu, Y., and Nagumo, T., 1991b, Antithrombin activity of a fucan sulfate from the brown seaweed

Ecklonia kurome. *Thromb. Res.,* 62(6), 765-773.

Ornitz, D.M., Herr, A.B., Nilsson, M., Westman, J., Svahn, C.M., and Waksman, 1995, FGF binding and FGF receptor activation by synthetic heparin-derived di- and tri saccharides. *Science,* 268, 432-436.

Shibata, H., Nagaoka, M., Takeuchi, Y., Hashimoto, S., Ueyama, S., and Yokokura, T., 1998, Anti-ulcer effect of fucoidan from brown seaweed, *Cladosiphon okamuranus* tokida. *Jpn. Pharmacol. Ther.,* 26, 1211-1215.

Shibata, H., Takagi, I.K., Nagaoka, M., Hashimoto, S., Aiyama, R., Iha, M., Ueyama, S., and Yokokura, T., 2000, Properties of fucoidan from *Cladosiphon okamuranus* tokida in gastric mucosal protection. *Bio Factors,* 11, 235-245.

Soll, AH., 1989, Duodenal ulcer and drug therapy. In: Sleisenger M.H., and Fordtran, J.S., eds. *Gastrointestinal disease*: pathophysiology, diagnosis, management. 4th ed. Philadelphia: Saunders, 814-879

Soll, A.H., 1990, Pathogenesis of peptic ulcer and implications for therapy. *N. Engl. J. Med.,* 322, 909-916.

Szabo, S., Kusstatscher, S., Sander, Z., and Sakoulas, G., 1995, Molecular and cellular basis of ulcer healing. *Scand. J.Gastroenterol.,* 30. Suppl. 208, 3-8.

Takagaki, Y.M., and Hota, K., 1979, Characterization of peptic inhibitory activity associated with sulfates glycoprotein isolated from gastric mucosa. *Biochem. Biophys. Acta,* 584, 288-297.

Takemoto, T., Sasaki, N., Tada, M., Yanai, H., and Okita, K., 1991, Evaluation of peptic ulcer healing with a highly magnifying endoscope: potential prognostic and therapeutic implications. *J. Clin. Gastroenterol.,* 13 (Suppl 1), S125-128.